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The frequency and associated factors of pulmonary fibrosis by the twelfth month after community-acquired pneumonia

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ABSTRACT

Aims: Community-acquired pneumonia (CAP) is a term used to describe an acute lung infection that develops outside of a hospital setting. Radiological sequelae may remain in a certain part of these patients that may affect their lives. We aimed to investigate the frequency of sequelae parenchymal lesions and influencing factors in patients with community-acquired pneumonia.

Methods: This retrospective study included patients diagnosed with CAP. First, patients who were admitted to the chest diseases outpatient clinic for any reason and who were treated with the diagnosis of CAP in the emergency department 12 months ago at the earliest were selected. Among these patients, patients with thorax computed tomography (chest-CT) under the control of the chest diseases outpatient clinic were included in the study. Chest-CT results, demographic data and laboratory data were evaluated.

Results: A total of 80 patients, 32 (40%) female and 48 (60%) male, diagnosed with CAP were included. The mean age of our patients was 56.83±13.41 (min-max: 18-71). Twenty-three (28.75%) of the patients did not have pathology in the control chest-CT, while 57 (71.25%) patients had various levels of sequelae changes. Of the sequelae observed in 57 patients, 34 (42.5%) had single linear atelectasis or single band formation or ectasia in a single bronchus, while fibrotic structure was detected in 23 (28.75%). Five (6.25%) patients had pulmonary fibrosis. Age and smoking have a statistically significant effect on the presence of fibrosis in patients with CAP.

Conclusion: Mild to severe fibrotic changes were observed in one-third of our patients one year after CAP treatment. In our study, fibrotic changes were found to be highly correlated with age and smoking.

Keywords: Pneumonia, fibrosis, age, smoking

INTRODUCTION

Pneumonia can be defined clinically and radiologically as the presence of signs of lung consolidation with acute infection of the lung parenchyma distal to the terminal bronchioles.[1] Community-acquired pneumonia (CAP) describes a lung infection that develops during daily life.[1] CAP is responsible for a significant proportion of physician admissions, treatment expenses, work-school day losses and deaths all over the world.[2,3] Although infectious disease related deaths are gradually decreasing due to the widespread use of antibiotics and effective immunization policies, CAP still high morbidity and mortality.[1] Pneumonia is the fourth common cause of mortality and the first common cause of mortality due to all infections in Turkey and worldwide.[1,4] CAP is the leading cause of morbidity and mortality in America, occurring in 649-847 adults per 100,000 population, causing approximately 1.6 million hospitalizations per year.[4]

In Turkey, pneumonia ranks first in deaths due to infection, and the mortality rate of pneumonia varies between 1-60% depending on the severity of the disease, and this rate increases significantly among hospitalized patients (10.3-60%).[5] According to the Ministry of Health statistics 2004, pneumonia accounted for 1.9% of all hospitalizations.[1] CAP risk factors are primarily defined as conditions that reduce the efficacy of the normal mechanisms of lung immunity. The predominant risk factors are age, chronic diseases and smoking.[6] The development of CAP is significantly associated with smoking. Passive smokers over 65years of age have an increased risk

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for CAP. An important dose-response relationship is evident for current smokers.[7] The frequency of pneumonia increases with age worldwide. McLaughlin et al.[8] found that, the rate of hospitalization for pneumonia was ten times higher in the elderly (>65 years of age) than in the younger population (about 2000 versus about 200 per 100,000 per year).

The accepted reference diagnosis in pneumonia should be based on detecting of pathogenic agents in lung specimens with suggestive clinical findings.[9] Early diagnosis and treatment of CAP is life-saving. In meta-analyses, it is stated that pneumonia treatment should be started within four hours and eight hours at the latest.[10] However; this cannot be accomplished in routine clinical practice for obvious practical reasons. Therefore, pneumonia is usually suspected when the person has complaints and signs of lung infection and is confirmed by the finding of a new infiltration area on radiological examination.[11]

The sequelae seen in pneumonia depend on the etiologic agent and the complications that develop during and after treatment. Linear bands, ectatic bronchial segments and fibrotic lung areas are observed in a particular proportion of patients with pneumonia.[12] These fibrotic structures and bands are known to be more common in viral infections, especially COVID-19.[13,14] Although some evidence suggests the role of viruses in the pathogenesis of pulmonary fibrosis, the role of bacteria is much less known; The only observational evidence was provided by Richter et al.[15] Infectious agents, including viruses and bacteria, can cause alveolar-epithelial cell damage and apoptosis. There are relatively few studies that have examined the role of infection in the development of pulmonary fibrosis. Those who have it point out that viruses play a crucial role as cofactors in the initiation and progression of fibrosis.[16]

Infections can induce pulmonary fibrosis by directly damaging the lung or causing damage through the immune system. After the pathogenic agent reaches the lung, inflammatory infiltration activates the immune system. Macrophages, neutrophils, eosinophils and Th^2 cells gather at the injury site, releasing numerous pro-inflammatory and pro-fibrotic cytokines/factors. The direct action of the pathogen and the combination of these factors promote pulmonary fibrosis, causing permanent and significant lung damage.[13] Molecular microbiological techniques emerging daily facilitate the study of microbial communities in the lung. Combining such techniques with careful longitudinal phenotyping of patients with pulmonary fibrosis makes it seems that it will be possible to elucidate the role of bacteria and viruses in the pathogenesis of the disease.[16]

Postinfectious parenchymal sequelae that develop in individuals may show loss of function according to the level of sequelae that develop in these individuals. We aimed to investigate the frequency of pulmonary fibrosis and other sequelae parenchymal lesions and and the factors affecting pulmonary fibrosis in patients with CAP.

METHODS

Participants and Study Design

The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (Date: 10.10.2023, Decision No: 2464). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included patients diagnosed with CAP. In this study, individuals over 18 years of age, regardless of gender who applied to the Chest Diseases Outpatient Clinic of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital between 01.08.2022 and 01.08.2023, were selected.

Firstly, patients who applied to the chest diseases outpatient clinic due to any complaint and underwent chest CT because pathology was detected in chest X-rays were selected for the study. The records of these patients were retrospectively analyzed using the hospital management system records. Twelve months ago, patients who received CAP treatment in the emergency department of our hospital were selected. Patients with complete file information at the time of initial CAP diagnosis (complaints, history information, examination findings, chest X-ray, computed tomography and laboratory tests) were included in the study. Patients with chest CT in the outpatient clinic of chest diseases were included in the study. Patients whose lung-CT reports were interpreted by the radiologist and whose reports were recorded in the hospital information system were also included in the study. In 2011, ATS, ERS, JRS and ALAT published a joint report and defined reticular densities, honeycomb findings (± traction bronchiectasis), predominant involvement of the subpleural and basal areas and the absence of findings incompatible with the usual interstitial pneumonia as interstitial fibrosis patterns.[17] Those with these radiological features were considered pulmonary fibrosis.

Patients with missing files, immune system disorders and malignancies were excluded. Also, patients with known interstitial lung disease and radiologically interstitial pathological appearance at the time of initial diagnosis of CAP were excluded. Patients medical records and charts were analyzed. Laboratory data of patients diagnosed with pneumonia; procalcitonin, C-reactive protein (CRP) and hemogram (neutrophil-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) were calculated and white blood cell (WBC) count value was examined). Due to the COVID-19 pandemic period COVID-19-PCR and other viral infection markers (respiratory syncytial virus, influenza, parainfluenza, adenovirus) were accepted as respiratory panels.

The x-ray/chest CT results of the patients received in the study in the emergency department were collected in 5 groups with the joint decision of the consultant (at least post-fellowship experience of ten years) participating in the study;

1-Pneumonia in one lobe,

2-Unilateral multisegmental pneumonia or bronchopneumonia,

3-Unilateral multilobar pneumonia,

4-Bilateral multisegmental pneumonia or bronchopneumonia,

5-Bilateral lobar pneumonia.

The chest CT results of the patients received in the study were evaluated in terms of sequelae lesions and collected in 5 groups;

0-Normal,

1-Single linear atelectasis/band formation, ectasia in a single bronchus,

2-Parenchymal fibrotic changes in the pneumonia area. The change area is less than the right middle lobe medial segment area,

3-Parenchymal fibrotic changes are present in the pneumonia area. The change area is more than the medial segment of right middle lobe but less than the entire right middle lobe,

4-Parenchymal fibrotic changes in the pneumonia area. The change area is more than the right middle lobe area.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software (version 17.0; IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to test the data distribution. Continuous variables are presented as mean±standard deviation (SD) for those with a normal distribution or median (minimum-maximum) for those without a normal distribution. Categorical variables are presented as numbers and percentages n (%).The chi-square test was applied to crosscheck categorical data. Independent risk factors affecting radiological changes were analyzed by logistic regression, and the ROC curve was used to evaluate the diagnostic sensitivity, specificity, and optimal cutoff value of each index. Kruskal Wallis test was used to compare numerical parameters according to fibrotic changes subgroups, since the data did not show normal distribution. All analyses were appreciated at a 95% confidence interval and significance was appreciated at $p<0.05$.

RESULTS

Demographic Characteristics

This study included 80 patients with clinically and radiologically diagnosed CAP, regardless of gender. The mean age was 56.8±13.4. Thirty-two (40%) were female and 48 (60%) were male. The mean body mass index of the patients was 28.8±5.9. Thirty-seven (46.2%) our patients had chronic diseases; 15 (18.7%) had hypertension, 15 (18.7%) had diabetes mellitus, 11 (13.7%) had coronary artery disease and 4 (5%) had chronic kidney failure. According to smoking habits, 29 (36.3%) patients were current smokers, 31 (38.8%) had quit smoking and 20 (25%) had never smoked (Table 1).

Clinical Characteristics and Laboratory Findings

The most common complaint was cough, 67 (83.75%) of patients. Chest pain was present in 47 (58.75%) patients and sputum in 56 (70.0%). In addition, 49 (61.25%) patients had a fever, 43 (53.75%) shortness of breath and 7 (8.75%) hemoptysis. Mean values of laboratory results: fasting glucose 140.46±61.1 g/dl, alanine aminotransferase 31.4±21.3 U/L, aspartate aminotransferase 39.34±28.5 U/L, urea 34.6±19.4 mg/dL, creatinine 0.98±0.6 mg/dl, lactic dehydrogenase 315.7±116.3 U/L, ferritin 373.79±298.2 ng/ml, procalcitonin 0.64±2.1 ng/ml, C-reactive protein 100.36±69.3 mg/L, white blood cell count 9.66±4.1 10^9/ml, Neutrophil-lymphocyte ratio 8.42±8.2, monocyte lymphocyte ratio 0.52±0.4, platelet lymphocyte ratio 246.58±185. SARS-COV2-PCR and viral infection markers accepted as respiratory panels in our hospital (respiratory syncytial virus, influenza, parainfluenza, adenovirus) were negative.

Table 1. Baseline demographic and laboratory findings of the study population

Characteristics	Patients (n=80)
Gender, n(%)	
Female	32 (40%)
Male	48 (60%)
Age, year, mean±SD (minimum-maximum)	56.8 ±13.4(18-71)
BMI, year, mean±SD	28.8±5.9
Smoking, n(%)	
Smoking	29 (36.3%)
Qut	31 (38.7%)
Never smoked	20 (25.0%)
Chronic diseases, n(%)	
Hypertension	15 (18.7%)
Diabetes mellitus	15 (18.7%)
Chronic kidney failure	4 (5.0%)
Coronary artery disease	11 (13.7%)
Chronic heart failure	5 (6.2%)
Laboratory parameters, mean±SD	
White blood cell (10^9/ml)	9,66 ± 4.1
Procalcitonin (ng/ml)	0,64 ± 2.1
C-reaktive protein (mg/L)	100,36 ± 69.3
NLR	8,42 ± 8.2
PLR	246.58 ± 185
MLR	0.52 ± 0.4

BMI: Body mass index, SD: Standard deviation, NLR: neutrophil-to-lymphocyte ratio,PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio

Radiological Findings

According to the radiological findings at the time of diagnosis of CAP in the emergency department: 36 (45%) patients had single lobe pneumonia, 9 (11.3%) unilateral multisegmental pneumonia or bronchopneumonia, 13 (16.3%) unilateral multilobar pneumonia, 14 (17.5%) multisegmental pneumonia or bronchopneumonia, and 8 (10%) bilateral lobar pneumonia. Patients with sequelae in chest CT taken during chest diseases outpatient clinic examination were divided into four groups. Chest CT was normal in 23 (28.8%) patients and 34 (42.5%) patients had single linear atelectasis/band formation and ectasia in a single bronchus. Eighteen (22.5%) patients had parenchymal fibrotic changes in the area where pneumonia was passed, the change area was less than the medial segment area of the right middle lobe. Three (3.8%) patients had parenchymal fibrotic changes in the area of pneumonia; the area of change was more than the medial segment of the right middle lobe but less than the entire right middle lobe, and 2 (2.5%) patients had pneumonia (Table 2).

Table 2. Distribution of sequelae lesions after 12 months based on the initial diagnosis

		Sequeale					
	n:80	**Normal n (%)**	**Single linear atelectasis/ band formation, ectasia in a single bronchus n (%)**	**Parenchymal fibrotic changes in the pneumonia area, the change area is less than the right middle lobe medial segment area n (%)**	**Fibrotic changes are present in the pneumonia area, the change area is more than the right middle lobe medial segment but less than the entire right middle lobe n (%)**	**Fibrotic changes in the pneumonia area, the change area is more than the right middle lobe area n (%)**	**Total n (%)**
First radiology	Pneumonia in one lobe,	14 (17.5)	18 (22.5)	4 (5.0)	4 (5.0)	0 (0)	36 (45.0)
	Unilateral multisegmental pneumonia or bronchopneumonia,	4 (5.0)	3 (3.75)	2 (2.5)	2 (2.5)	0 (0)	9 (11.25)
	Unilateral multilobar pneumonia	2 (2.5)	6 (7.5)	5 (6.25)	5 (6.25)	0 (0)	13 (16.25)
	Bilateral multisegmental pneumonia or bronchopneumonia	3 (3.75)	5 (6.25)	4 (5.0)	4 (5.0)	0 (0)	14 (17.5)
	Bilateral lobar pneumonia.	0 (0)	2 (2.5)	3 (3.75)	3 (3.75)	2 (2.5)	8 (10.0)
	Total	23 (28.75)	34 (42.5)	18 (22.5)	3 (3.75)	18 (22.5)	80 (100)

In Table 2, 23 (28,7%) patients did not have pathology in the control chest CT, while 57 (71.3%) patients had various levels of sequelae changes. Of the sequelae observed in 57 patients, 34 (42.5%) had single linear atelectasis or single band formation or ectasia in a single bronchus, while 23 (28.7%) showed fibrotic structure. Five (6.25%) patients showed signs of pulmonary fibrosis.

Correlation Analyzes of Radiological Lesions

Risk factors were evaluated for developing sequelae lesions and fibrosis. Age and smoking had a statistically significant effect on the development of fibrosis in CAP patients. This was statistically significant ($p < 0.05$). No effect was found between gender, CRP, NLR, MLR or PLR and the development of fibrosis in patients with CAP ($p > 0.05$) (Table 3).

A relationship was found between the CAP patients' age and the fibrotic changes The cut off value was 55.5 with a sensitivity of 77.2% and a specificity of 82.6% for age, which was statistically significant (Logistic Regression Analysis; $p=0.0001<0.01$). Change in age explains 36.4% of the presence of fibrosis. A one-unit enhancement in age increases the existence of fibrosis by 1.112 times. The effect of age risk factor on fibrotic changes is demonstrated by ROC analysis.

Table 3. Analysis of logistic regressions examining the impact of risk factors on radiological sequelae

Fibrosis risk factors	**x^2**	**p (Model)**	**-2 Log likelihood**	**R^2**	**B**	**Standard deviation**	**Wald**	**sd**	**p**	**Exp(B)**
Age	23.481	0.0001**	72.503	0.364	0.106	0.027	15.053	1	0.0001	1.112
Gender	0.01	0.92	95.973	0	0.051	0.505	0.010	1	0.92	1.052
Smoking	9.667	0.002**	86.317	0.163	1.094	0.383	8.142	1	0.004	2.986
CRP	3.727	0.054	92.257	0.065	0.008	0.004	3.125	1	0.077	1.008
NLR	3.514	0.061	92.47	0.061	0.086	0.057	2.283	1	0.131	1.090
MLR	0.307	0.579	95.677	0.005	-0.332	0.591	0.315	1	0.575	0.718
PLR	0.377	0.539	95.607	0.007	0.001	0.001	0.354	1	0.552	1.001

The vertical axis: Fibrosis risk factors, the horizontal axis: Statistical analysis values. Abbreviations: CRP: C-reactive protein, NLR: neutrophil-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, PLR: platelet-lymphocyte ratio,** statistically significant.

DISCUSSION

In this study, it was shown that two-thirds of the patients treated for CAPP had radiological sequelae. One year after CAP treatment, mild to severe fibrotic changes were observed in two-third of our patients. Minimal changes were observed in about one-third of patients, while moderate to severe fibrotic changes were observed in one-fourth of the patients. Five patients showed signs of pulmonary fibrosis. In our study, fibrotic changes were found to be highly correlated and smoking. Procalcitonin, CRP, NLR, MLR and PLR values had no predictor effect of on the development of fibrosis in CAP patients.

Presently, literature studies in the world have focused on the etiology, risk factors and related treatment strategies of CAP. The pathogen often seen in CAP is Streptococcus pneumonia.[18] Most radiological changes mentioned in studies have been

with age shown in viral pneumonia cases.[13,14] Our study is important in demonstrating radiological changes in a disease in where the major pathogen is bacteria. The diagnosis of CAP and therefore the rate of hospitalization have been shown to be higher in the older adults than in the younger.[8] In addition, smoking is a strong and independent risk factor for progressive pneumococcal disease in all age groups.[19] It is important to show the effect of these two factors on the sequelae that develop due to CAP.

After a lung infection, it is essential to repair the tissue architecture to regain the normal organ function of the lung. Pulmonary fibrosis and the associated remodeling of the lung can severely impair lung function and often have fatal consequences. Wilson and Wynn described the mechanisms of the development of pulmonary fibrosis in their review. In this review, they collected inflammation and healing in 3 stages (1-Injury, 2-Inflammation, 3-Fibroblasts contract) and stated that slowing or deficiency in any of these stages causes deterioration of tissue architecture.[20] Molyneaux and Maher investigated the pathogenesis of IPF. They said that bacteria and viruses have the potential to cause bronchial and alveolar epithelial cell damage and apoptosis and have the capacity to regulate the host response to damage in both types of agents.[16] **A**n article showed that individuals with lung fibrosis had a high bacterial load in the BAL fluid.[21] In our study, about a quarter of patients did not detect any pathology on chest CT after one year. Thirty-four patients had parenchymal changes, defined as 'single linear atelectasis or single band formation or ectasia in a single bronchus, which we did not associate with fibrosis. In eighteen patients, there were fibrotic changes in the pneumonia area and the area of change was less than the medial segment area of the right middle lobe. Five patients showed signs of pulmonary fibrosis.

Biological lung aging is characterized by structural changes and advancing loss of physiological totality, which leads to dysfunction. Although the mechanisms contributing to the aging process are unclear, nine putative distinguishing characteristics associated with the aging phenotype have recently been proposed. It is not accepted how these features contribute to the aging lung.[22] Studies have shown that aging imparts a profibrotic phenotype to fibroblasts and increases the severity of the fibrogenic response in IPF and non-IPF fibrotic lung disorders.[23,24] Delgado et al.[25] reported that NLRP3 inflammatory activity and oxidative stress increased with age contributing to the improving of pulmonary fibrosis. A review, it was stated that aging is related to a wide range of biological changes and is therefore a critical risk factor for pulmonary fibrosis. In the article, it is said that the improvement of pulmonary fibrosis is the result of multiple processes working together, including environmental and metabolic factors such as epigenetic, transcriptional, posttranscriptional, and often infection, in individuals who are susceptible or genetically predisposed due to aging.[26] Age had a statistically prominent effect on fibrosis in patients with CAP. Change in age explains 36.4% of the presence of fibrosis. A one-unit increase in age increases the presence of fibrosis by 1,112 times. ROC analysis showing the link between age and sequelae-fibrosis is observed in Figure.

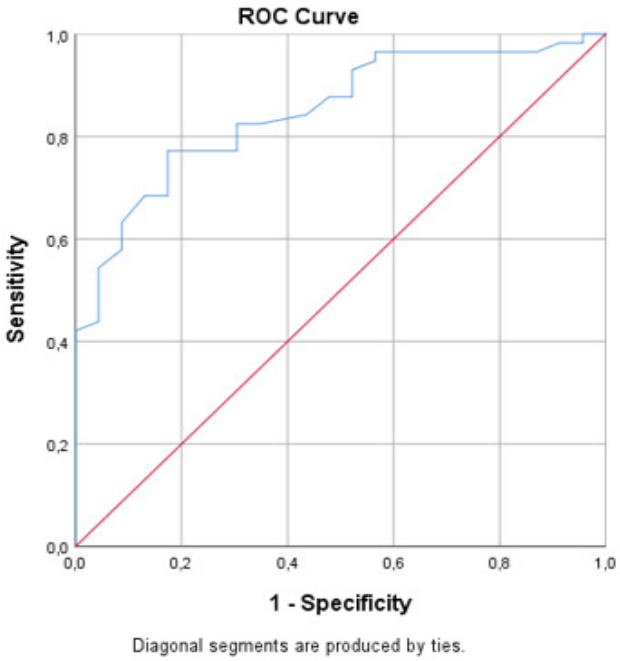

Figure. Demonstration of the effect of age risk factor on fibrotic changes by ROC analysis
* Sensitivity: 77.2%, Specificity: 82.6%, cut off: 55,5, Area Under Curve: 0,84(0,76;0,93)

Although numerous studies indicate that smoking subscribes to the development of lung fibrosis, it is not known how it subscribes to the pathogenesis of fibrosis. Among the risk factors for developing fibrosis, smoking appears to be the most potent risk factor with both sporadic and familial pulmonary fibrosis.[27] In the study, Bellou et al.[28] observed a dose-reply relationship between pack-years of smoking and lung fibrosis in smokers (HR per 1-pack-year increase, 1.013; 95% CI, 1.009–1.016). In a review, it was concluded that smoking increased the development of pulmonary fibrosis with a odds ratio of 1.39 (95% CI 1.01–1.91, I 2=29%).[29] Again, in a comprehensive review, it was stated that smoking is a well-known etiological factor linked to the development of lung cancer, obstructive pulmonary diseases and various types of interstitial lung disease.[30] In this review, it is emphasized that smoking contributes to the formation of fibrosis in the lungs and that both genetic and exogenous triggers such as allergens or infections play a role in this process. Smoking has a statistically considerable effect on the existence of fibrosis in our patients with CAP. Smoking explains 16.3% of the presence of fibrosis. Smoking increases the presence of fibrosis by 2.986 times.

Apart from age and smoking risk factors, we investigated the correlation of biomarkers performed in the emergency department at the time of diagnosis that may affect the development of fibrosis. There was no statistically prominent effect of procalcitonin, CRP, NLR, MLR and PLR values on the presence of fibrosis in our patients with CAP who participated in the study.

Limitations

Our study had several limitations. The most notable constraint was the absence of recorded medical histories. A considerable number of pneumonia patients were ineligible for inclusion in the study due to the absence of radiological

images. The second major limitation is that although a lot of CAP is diagnosed in the emergency department, diagnosis and treatment are performed without adequate confirmatory examination due to the patient density. This lack of examination may cause diagnosis and treatment errors. This caused the number of patients in the study to be less than expected.

CONCLUSION

As we know, community-acquired pneumonia is an infectious disease that affects all segments of society. Studies have mainly focused on its etiology and treatment. We investigated the frequency of fibrosis development, which is one of the outcomes of this disease. One year after undergoing CAP, bronchiectasis and atelectasis were observed in one-third of our patients. About one-third of them had mild to severe fibrotic changes. Fibrotic changes were highly correlated with age and smoking. More studies should be conducted on the sequelae fibrotic changes observed in patients. Our follow-ups continue to show long-term progression.

ETHICAL DECLARATIONS

Ethical Approval

This study was approved by the Ethics Committee of the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital (10.10.2023/2464).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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